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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,410	MARTUZA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-20 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/26/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 18, 2008 has been entered.

Claims 1-15, 17, and 21-27 are cancelled. Claims 16 and 19 are amended. Claims 16, 18-20 and 28-32 are pending and currently under examination.

This application 10/788,410 file don 03/01/2004 is a DIV of 09/625,509, filed on 07/25/2000, now PAT 6,699,468, which is a DIV of 09/004,511, filed on 01/08/1998, now PAT 6,139,834, which is a CON of 08/478,800, filed on 06/07/1995 ABN, which is a CON of 08/264,581, filed on 06/23/1994, now PAT 5,585,096 (changes are in bold for emphasis). The series of parent applications of instant application listed above is based on the Application Data Sheet filed on 08/06/2007.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Previous rejection of claims 16, 18-20, and 28-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claim 16 has been amended and no longer recites the limitation "the mutation" as there is insufficient antecedent basis for this limitation in the claim. Claims 18-20, and 28-32 depend from claim 16.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous scope of enablement of claims 16, 18-20 and 28-32 under 35 U.S.C. 112, first paragraph, is ***withdrawn*** because the claims have been amended to address that the specification, while being enabling for a herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated, and for said virus further comprising at least one further gene alteration in ribonucleotide reductase (RR) gene such that no functional ribonucleotide reductase is made, **does not** reasonably provide enablement for a herpes simplex virus with a genome comprising 1) any alteration in the γ34.5 gene and the ribonucleotide reductase gene other than an alteration that results in a lack of function of each gene product, or 2) for a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence.

Claim 16 has been amended as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

Claims 18-20 and 28-32 depend from claim 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 16, 28, and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994). Applicant's arguments filed 12/18/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 11-14 of the office action mailed on 02/14/2008 and elaborated on pages 6-13 of the Final office action mailed on 08/18/2008.

Claim 16 has been amended as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

For clarity and completeness of this office action, the reasons of record advanced on pages 6-13 of the office action mailed on 08/18/2008 is reiterated below.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Roizman et al. teaches the following: **(i)** Novel modified HSV vectors for gene therapy (See abstract, Roizman et al., 2001), which reads on the limitation "an expressible non-herpes simplex virus nucleotide sequence" recited in claim 16 of instant applicant application, **(ii)** The function of the gene γ34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-

pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001), **(iii)** The use of the HSV-1 virus with a null mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the γ34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on the limitation of claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001), and **(iv)** The embodiment of the present invention describes a method which involves combining ICP34.5 (i.e. γ34.5) or a biological functional equivalent thereof with a pharmaceutically acceptable carrier in order to form a pharmaceutical composition, which reads on claim 29 of instant application.

Roizman et al., do not teach do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene recited in claim 16.

Vile et al. teaches that (i) transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), and (ii) constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See

conclusions, right column, second paragraph, Vile et al., 1994), and that (iii) use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roizman et al. (2001) regarding the characteristics of a mutant herpes simplex virus comprising a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, with the teachings of Vile et al. (1994) regarding exogenous expression of a cytokine gene results in diminishment or elimination of tumorigenicity of tumor cells via elicitation of immune response to arrive at the claimed HSV with disrupted both γ34.5 that exhibits no neurovirulence, and expressing a cytokine gene that elicit an immune response against a tumor cell, as recited in claims 16, 28, and 29 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994) because (i) the γ34.5 gene mutation would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), and (ii) the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the

demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments***

(i) Applicant argues that Roizman and Chang actually would have informed the skilled artisan only that an HSV mutant may be used in oncolytic therapy, since the mutant HSV is able to infect dividing cells, such as cancer cells, while leaving the normal, un-dividing cells unharmed. On the other hand, Vile taught *in situ* gene therapy using cytokines, but the reference would not have suggested expression of a cytokine in the context of an oncolytic virus such as HSV. That is, Vile discloses direct injection of cytokine-encoding DNA, under the control of a tumor-specific promoter, into established tumors of mice, resulting in cytokine expression (see "Summary" and Figures 4b and 4c). Vile concludes that "[n]o statistically significant reduction in tumor growth was seen following injection of any of these cytokine expression plasmids..." (page S62, right column, lines 9-12 and figure 4a) (See page 5 of Applicant's remarks filed on 12/18/2008).

Applicant argues that Vile was published in 1994; hence, it evidences the state of the art at the priority date of the present application. At the time of publication, according to Vile, "such in situ gene therapy [as described above] would require a specificity of gene delivery that is ***impossible using currently available viral vectors*** or physical transfer techniques" ("Introduction" at page S59, left column in lines 12-15; emphasis added). Vile attempted to

address this contemporaneous "impossibility" by using a tumor-specific promoter to direct expression of cytokine genes, but failed to achieve any therapeutic effects, as noted above. Thus, Vile admitted that, "[t]o date, a significant anti-tumor effect on the growth of the injected tumors using cytokine cDNAs has not been observed," and that "[t]his is not wholly unexpected" (page S64, left column, lines 14-16). Applicant argues that at the time of filing, therefore, the prior art made no suggestion of expressing a cytokine with an oncolytic virus, and such a combination would have contravened the conventional wisdom of the day and, hence, was anything but obvious (See pages 5-6 of Applicant's remarks filed on 12/18/2008).

In response, Applicant's arguments based on the asserted deficiency of Vile et al has been fully considered and found not persuasive because the *prima facia* obvious rejection is based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (*Ann Oncol.* 5 Suppl 4:59-65, 1994), rather than based on anyone of the tow individual references alone. Vile et al. is relied on for the teachings regarding the recited limitation "an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine". Applicant is reminded that, as stated in the maintained rejection under *Claim interpretation*: The limitation "capable of eliciting an immune response against a tumor cell" recited in claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. Furthermore, claim 16 is a product claim, a HSV with null mutation of both γ34.5 and ribonucleotide reductase and a cytokine gene inserted in the HSV genome. Whether the expression of a cytokine alone can lead to a statistically significant reduction in tumor growth, as discussed by Vile et al., is not required by the claimed product. Related to this discussion, as

stated in the maintained rejection, Vile et al. teaches that transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994). Furthermore, as disclosed by Vile et al., the goal of cancer gene therapy is to target specifically to cancer cells, and Vile et al. teaches using tumor-specific promoter to overcome non-tumor cell specific expression of gene of interest. Bearing the goal of targeting specifically to cancer cells, it is noted that the teachings of primary Roizman et al. is focusing on using mutant HSV as a vector for cancer gene therapy (i.e. introduction of gene of interest for therapeutic purpose). Therefore, a skilled person in the art would certainly be motivated to incorporate the teachings of Vile et al. in the context of non-pathogenic HSV taught by primary reference Roizman to arrive at the claimed the HSV with recited genome in claims 16, 28, and 29 of instant application.

(ii) Applicant argues that PTO's combining of cited references is informed by hindsight, not by suggestion in the prior art because that the gene-therapy paradigm of the prior art contrasts sharply with the approach of the present invention. The latter employs an oncolytic viral (HSV) vector that is replication-competent; hence, the vector is not mere delivery vehicle but rather is a *de facto* active agent, killing host cells (See page 6 of Applicant's remarks filed on 12/18/2008).

In response, the primary reference Roizman teaches oncolytic viral (HSV) vector being replication-competent, which is certainly not by hindsight as Applicant argues. Specifically, as

stated in the maintained rejection, Roizman teaches the use of the HSV-1 virus with a specific mutation in the gamma34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "gamma34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the gamma34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001).

(iii) Applicant argues that evidence of record that the purported combination would have contravened conventional wisdom. Applicant states that during previous run of prosecution, Applicants have made of record a Rule 132 declaration by inventor Rabkin, attesting that those in the field would not have considered it obvious to express cytokines in the HSV, given the known protective effects of cytokines for HSV. Applicant states that, rather than contesting the declaration evidence directly, however, the Examiner is heard to contend that the evidence is not probative of patentability because, pursuant to the claimed invention, a cytokine gene would not be expressed until after the HSV vector infected targeted cells.

Applicant argues, again, that the Examiner's discounting of the declaration evidence is based on 20/20 hindsight. Applicant argues that the skilled person would have understood that expression of cytokine and the resultant elicitation of an immune response require the existence of an intact, functioning target cell. On the other hand, infection with an oncolytic HSV of the claimed invention kills the target cell. Thus, the contemporaneous teachings of the cited art (as opposed to the present teachings of Applicants' specification) would have prompted the skilled

artisan not to consider an "expressible," cytokine-encoding "nucleotide sequence," as presently recited, as a feasible component for a herpes simplex virus vector. Applicant argues that the prospect of combining the prior-art teachings invoked by the Examiner would have presented the skilled artisan with several scenarios, each fraught with a priori uncertainty:

(A) The expression or secretion of the cytokine could induce an anti-HSV immune response, which threatens the elimination of HSV-infected tumor cells before the HSV replicates and spreads. The oncolytic effect of HSV would be lost as a consequence, and the immune effect would be equivalent to that of a cytokine gene therapy approach where immunization against tumor antigens is intended.

(B) The replication of HSV, leading to apoptosis and/or cell lysis, is rapid enough to parallel an anti-HSV response that the cytokine induces. Accordingly, the virus still is able to spread and, while it alerts the immune system to viral antigens, it also induces an anti-tumor immune response.

(C) The replication of HSV leads to apoptosis or cell lysis before the release of a sufficient amount of expressed cytokine, thereby realizing benefit from oncolytic therapy only. Which of these scenarios might prevail was entirely unpredictable, in view of contemporaneous state of the art. Applicant argues that this lack of predictability also is sufficient unto itself to defeat the notion that the claimed HSV is obvious within the meaning of Section 103.

Applicant argues that in view of the foregoing, it is apparent that Applicants' declaration evidence stands effectively unrebutted on the record, and for this reason, too, withdrawal of the obviousness rejection in question is warranted.

In response, Applicant's arguments pertaining to the Declaration by inventor Rabkin, attesting that those in the field would not have considered it obvious to express cytokines in the HSV, has been addressed on pages 14-15 of the Final office action mailed 08/18/2008. In short, the Declaration by inventor Rabkin focuses on the effect of endogenously expressed cytokine in elicitation of protective immunity, however, in the claimed HSV, a cytokine gene would not be expressed until after the HSV vector infected targeted cells. Furthermore, as elaborated below, the efficacy of the claimed HSV in cancer gene therapy is the intended use of the claimed HSV.

The Examiner notes that to the Examiner's best knowledge, conventional wisdom (which Applicant appears to refer to reports cited in the Declaration by inventor Rabkin) is not the sole driving force to be relied on for scientific discovery and innovation. It is not uncommon that expression of a protein (cytokine, in this case) may result in multiple effects. For instance, expression of cytokine endogenously has been reported to elicit protective immunity under normal physiological conditions (the essence of Declaration by inventor Rabkin) and expression of exogenous cytokine in cancer cells leads to activation of immune system which in turn eliminate cancer cells (reported by Vile et al. cited in this 103 rejection).

The Examiner acknowledges that the intended use for cancer gene therapy of the HSV recited in the claims of instant application may function in multiple possible scenarios, including (A) to (C) discussed by Applicant. The Examiner also acknowledges that even as of current status of art, the outcome of cancer gene therapy in general remains unpredictable and needs to be evaluated on a case-by-case basis. However, it is worth emphasizing, again, the claims of instant application is directed to a product, not a method of using said product in cancer gene therapy that results a statistically significant reduction in tumor growth, as Applicant argues. In

this regard, as stated in the response under **(i)** section, claim 16 is a product claim, a HSV with null mutation of both γ34.5 and a cytokine gene inserted in the HSV genome. The structure and inherent properties of the structure of claimed HSV as a whole was clearly *prima facie* obvious based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (*Ann Oncol.* 5 Suppl 4:59-65, 1994). The efficacy of the claimed HSV in cancer gene therapy is the intended use of the claimed HSV, which the Examiner agree with Applicant that the intended use of the claimed HSV in treating a given cancer remains unpredictable as Applicant argues that several possible scenarios may occur. Nevertheless, a skilled person in the art would be motivated to make the claimed HSV based on the combined references and to test how effective the claimed HSV may be in cancer gene therapy.

5. Claims 16, and 18-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claims 16, 28, and 29 above, and further in view of **Chang et al.** (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991). Applicant's arguments filed 12/18/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-17 of the office action mailed on 02/14/2008 and elaborated on pages 14-17 of the Final office action mailed on 08/18/2008.

For clarity and completeness of this office action, the reasons of record advanced on pages 14-17 of the office action mailed on 08/18/2008 is reiterated below.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. It is noted that in the art G207, as recited in claim 20 of instant application, is the name of an HSV that contains deletions of both copies of the gamma34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

For clarity and completeness of this office action, the reasons of record advanced on pages 14-17 of the office action mailed on 08/18/2008 is reiterated below.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene (recited in claim 19 of instant application).

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene was known in the art. For instance, Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that

ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial LacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir, hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of *a foreign gene* (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine (i) the characteristics of a mutant herpes simplex virus comprising an nucleotide sequence encoding a cytokine, a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, as taught by combined teachings of Roizman et al. 2001 and Vile et al., 1994, with (ii) the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001, and Vile et al., 1994, with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 16 and 18-20 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001, Vile et al., 1994, with the teachings of Chang et al. 1991 because the disrupted γ34.5 gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, and (3) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al. Furthermore, regarding the motivation to combine the cited reference, it is worth adding that, bearing the goal of targeting specifically to cancer cells taught by Roizman et al. and Vile et al., Chang et al. teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of *a foreign gene* (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991).

6. Claim 30-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claim 16, 28, and 29 above, and further in view of **McKay et al.** (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and **Wright, Jr.** (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994). Applicant's arguments filed 12/18/2008 have

been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 17-20 of the office action mailed on 02/14/2008 and elaborated on pages 18-22 of the Final office action mailed on 08/18/2008.

For clarity and completeness of this office action, the reasons of record advanced on pages 18-22 of the office action mailed on 08/18/2008 is reiterated below.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that expresses a exogenous cytokine gene, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, or epidermal growth factor (EGF) promoter, as recited in claims 30-32 of instant application.

At the time of filing of instant application, it was known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression

as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, Jr. 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997). Furthermore, as indicated before, Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001). Accordingly, it would have been *prima facie* obvious the nestin promoter, bFGF promoter, EGF promoter are tumor cell specific promoters, and thereby can be used for expressing an essential viral gene as recited in claims 30-32 of instant application by the combined teachings of Roizman et al., 2001, McKay et al., 1991, and Wright, 1997.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a nucleotide sequences encoding a cytokine, whose transduction of tumor cells with cDNAs encoding various cytokines has been shown to diminish or eliminate tumorigenicity in syngeneic animals, in a γ34.5 defective HSV vector, as taught by the combined teachings of Roizman et al., 2001 and Vile et al., 1994, and to have an essential viral gene product under the control of a tumor cell-specific promoter of nestin or bFGF, or EGF, as taught by the teachings of Wright or McKay et al., in the said herpes simplex virus vector with disrupted both γ34.5 and expressing nucleotide sequences encoding a cytokine, to ensure that the said HSV vector exhibits no neurovirulence and specifically

infecting the fast dividing cancer cells in the cancer cells, by the combined teachings of Roizman et al., 2001, Vile 1994, and Chang et al., 1991.

It would have been obvious at the time of filing to combine (i) the teachings of Roizman et al. 2001, and Vile et al., 1994, regarding a HSV vector for cancer treatment with the expression of a nucleotide sequences encoding a cytokine from a HSV vector, wherein as essential viral gene product placed under a suitable target specific promoter, with (ii) the teachings by Wright or McKay et al., regarding gene product being under the control of the tumor specific promoters of nestin or bFGF, or EGF to arrive at the claimed herpes simplex viruses as recited in claims 30-32 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, expresses nucleotide sequence encoding a cytokine, and infects specifically to tumor cells, by combined teachings of Roizman 2001, Vile et al., 1994, to introduce the expression of a nucleotide sequences encoding a cytokine for gene therapy, and said HSV vector comprises an essential gene product under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., becasue the HSV vector being non-pathogenic and specifically infect tumor cells without harming healthy cells, and the exogenous nucleotide sequence encoding cytokine is expressed only in the tumor cells, as an essential viral gene product is expressed in a tumor specific manner.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the

demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, (3) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
Art Unit 1632